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COMMUNICATION

An Ambient Pressure, Direct Hydrogenation of Ketones

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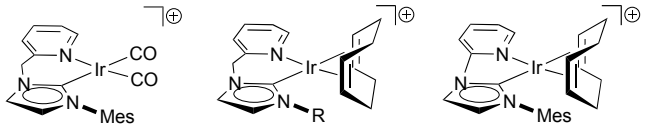
We report two bifunctional (pyridyl)carbene-iridium(I) complexes that catalyze ketone and aldehyde hydrogenation at ambient pressure. Aryl, heteroaryl, and alkyl groups are demonstrated, and mechanistic studies reveal an unusual polarization effect in which the rate is dependant of proton, rather than hydride, transfer. This method introduces a convenient, waste-free alternative to traditional borohydride and aluminum hydride reagents.

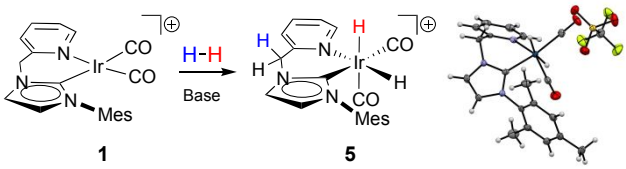
Direct hydrogenation of carbonyl groups is a 100% atom efficient, environmentally benign synthetic process. While hydride reagents like $LiAlH_4$ and $NaBH_4$ are effective and expedient for this transformation, these are accompanied by the cost and separation issues that accompany a stoichiometric portion of any metallic reagent, which makes direct hydrogenation an important option at scale.[1] Since Noyori's milestone discovery of asymmetric ketoester direct hydrogenation,[2] many well-defined molecular catalysts for hydrogenation, transfer hydrogenation, and dehydrogenation of C=O systems have emerged,[3] yet most rely on hydrogen gas pressure or a hydrogen donor/acceptor to obtain useful rates.[4] Frustrated Lewis-pair species have also been demonstrated,[5] although also rely on elevated gas pressure.[6] Such requirements for pressurization limit the utility of these methods and make them inconvenient for users without pressurization tools. Base metals (Fe, Co, Ni, and Cu) are emerging in this space;[7] in fact, the Hanson PNP–Co complexes catalyze ambient pressure hydrogenation of some ketones in THF at 60 °C,[7b] but room remains to introduce high reactivity, highly functional group tolerant catalysts for ambient pressure carbonyl hydrogenation. Thus, we report here a catalytic hydrogenation system that affects carbonyl hydrogenation with ambient hydrogen pressure at up to quantitative yield on a diverse set of ketones and aldehydes.



1 **2** R = Me **3** R = Mes **4**

Chart 1 Four iridium-based catalyst precursors. Anion = TfO^-.

We previously reported complexes **1**-**3** as pre-catalysis for glycerol dehydrogenation.[8] Therein we found that backbone deprotonation of **2** with concurrent pyridine dearomatization plays a mechanistic role in cleaving glycerol's O—H bond, apparently through a metal-ligand cooperative step. We further found that electron withdrawing CO ligands slowed dehydrogenation by comparing rates of reactions of **1** and **3**. We propose that the opposite should be true in the reductive direction, and that the apparent bifunctional nature of the backbone of **1**-**3** could facilitate H_2 cleavage as highlighted in Scheme 1.[3d]



1 **5**

Scheme 1 Hydrogen molecule cleavage and dihydride iridium formation, ORTEP diagram of **5** (CCDC 2142636) with 50% ellipsoids.

When we treated precursor **1** with KO^tBu and one bar H_2 in a J. Young tube at room temperature, we found that it rapidly split hydrogen and formed iridium dihydride complex **5** (Scheme 1).[9] The same reaction is unsuccessful with iridium complex **4** that lacks a pyridyl methylene arm, which is consistent with our view that the backbone CH group is important to hydrogen cleavage.

Whereas complexes **1-3** cleave H_2 at ambient temperature and pressure as shown in Scheme 1, we screened them for

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Electronic Supplementary Information (ESI) available: Synthesis and characterizations of all new compounds, kinetics studies, calculations, CIF data for **5**. CCDC 1438247 (**2**), 1438246 (**3**), 2142636 (**5**), and 2258133 (**6**) contain supplementary crystallographic data for the corresponding compounds. See DOI: 10.1039/x0xx00000x

ambient pressure acetophenone hydrogenation. Complex **1** has the highest reactivity among the three (Table S1). By contrast, complex **4** has no reactivity in acetone hydrogenation, again consistent with a role for the backbone CH group. Further consistent, none of these four iridium complexes has reactivity for acetone hydrogenation if base is removed from this reaction, although the role of the base could be to deprotonate a coordinated H_2 ligand. We therefore expect that ligand deprotonation and dearomatization play a role in hydrogen splitting and catalyst precursor activation for these precursors.

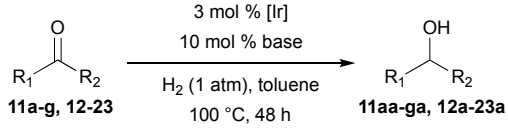
Condition optimization for the hydrogenation of acetophenone with **1** are outlined in Table S1. Various bases were tested for the hydrogenation of acetophenone, using 3 mol % **1**, 10 mol % base and 1 atm hydrogen pressure at 40 ° C. This taught us that effective bases have a pKa above ca. 16, which is appropriate for ligand backbone deprotonation: KO^{t}Bu, KH, and NaOEt afforded productive reaction where KOH and K_2CO_3 did not. We next turned to solvent and temperature. Increasing the temperature provided a modest increase in the reaction yield, but the yield at 120 ° C is lower than that at 100 ° C, thus leaving toluene as a suitable solvent for this reaction system. Gratifyingly, the system operates efficiently down to ambient pressure.

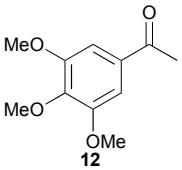
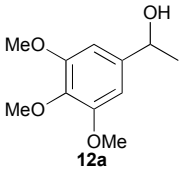
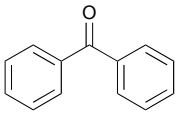
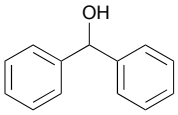
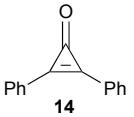
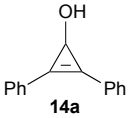
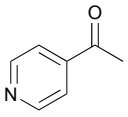
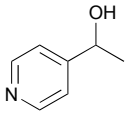
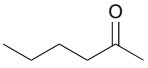
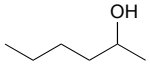
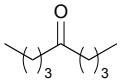
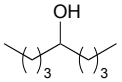
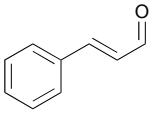
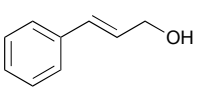
With optimized reaction conditions, we screened a series of ketones and aldehydes to understand the rection's scope. Studying a series of differentially *para*-substituted acetophenones (Table 1, entries 1-7) enabled calculation of a *negative* (nucleophilic substrate) Hammett reaction parameter of ρ = -0.93 (see Supporting Information). This negative ρ value is atypical for reduction, which should normally involve an electrophilic accepter receiving a nucleophilic hydride in a kinetically-relevant step: for example, the ρ value for $NaBH_4$ reduction of this reaction is +3.06,[10] and $LiAlH_4$ reduction of benzophenones +1.95.[11] Catalytic ketone hydrogenation with the Shvo system has ρ = +1.77, +0.91 under two conditions studied.[12,13] These undergo a concerted, outer-sphere hydrogen transfer mechanism. The ρ for Noyori type catalyst [$RuCl_2$(diphosphine)(1,2-diamine)] is ρ = +1.03.[14] Lewis acid-catalyzed acetophenone hydrogenation also has a positive ρ > 1.[15]

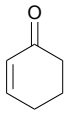
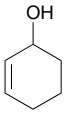
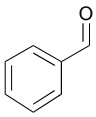
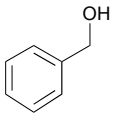
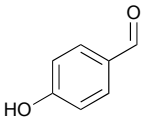
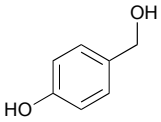
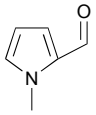
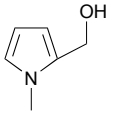
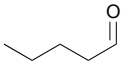
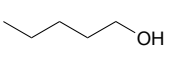
The negative ρ value in our system is consistent with kinetic relevance of a proton transfer step, rather than a hydride transfer as in the above cases. Its magnitude, ρ < -0.5, is consistent with the involvement of an anionic phenonone-containing fragment in or before our rate-limiting step.[16] Such a species could be a metal alkoxide,[17] which is protonated in a slow step (vide infra).

Continuing our study of substrate scope (Table 1), we examined ketones with increased steric demand. These are well tolerated (entries 8—9). Particularly, benzophenone was reduced at the larger 500 mg scale (entry 9b) to show that scaling the biphasic reaction does not significantly retard the yield. Furthermore, we tested the hydrogenation of benzophenone using conditions that did not involve our glove box, which we use for convenience in other cases. In entry 9c, all reagents were weighed out on the benchtop, and then the Schlenk flask was purged with H_2. This result shows that the

Table 1 Substrate scope.



Entry	Substrates	Products	[Ir]	Yield (%)[a]
1	R = H **11a**	R = H **11aa**	**1**	68
			6	>95
2	R = NMe_2 **11b**	R = NMe_2 **11ba**	**1**	>95
			6	>95
3	R = OMe **11c**	R = OCH_3 **11ca**	**1**	83
4	R = OH **11d**	R = OH **11da**	**1**	>95
5	R = Br **11e**	R = Br **11ea**	**1**	40
			6	81
6	R = Cl **11f**	R = Cl **11fa**	**1**	42
			6	83
7	R = NO_2 **11g**	R = NO_2 **11ga**	**1**	9[b]
8	 **12**	 **12a**	**1**	77
9	 **13**	 **13a**	**1**	85 77[c] 84[d]
10	 **14**	 **14a**	**1**	48
			6	88
11	 **15**	 **15a**	**1**	64
			6	89
12	 **16**	 **16a**	**1**	33
			6	72
13	 **17**	 **17a**	**1**	21
14	 **18**	 **18a**	**1**	73[b]

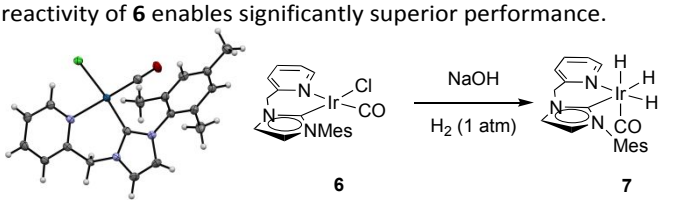
Entry	Substrates	Products	[Ir]	Yield (%)[a]
15	 **19**	 **19a**	**1**	32[b]
16	 **20**	 **20a**	**1**	>95
17	 **21**	 **21a**	**1**	>95
18	 **22**	 **22a**	**1** **6**	43[b] 85[b]
19	 **23**	 **23a**	**1** **6**	52[b] 80

[a]Isolated yield, 100 mg substrate scale. [b]NMR yield. [c]500 mg scale. [d]Reagents weighed out in air.

glove box is not necessary for this system, thus making it practically accessible to organic practitioners. Diphenylcyclopropenone was reduced chemoselectively at the C=O bond, with no evidence of C=C reduction (entry 10). Heteroaryl-substituted ketones and aldehydes were also hydrogenated (entries 11, 18). For aliphatic ketones such as 5-nonanone and 2,2,4,4-tetramethyl-3-pentanone, lower activity was observed (entries 12, 13).

To gain insight into the chemoselectivity of reactions of catalyst **1**, a competition experiment was performed in which a 1:1 mixture of styrene and benzaldehyde was hydrogenated using **1**. Benzaldehyde was hydrogenated more rapidly, with complete conversion of benzaldehyde and only 8% conversion of styrene observed over 48 hours. We can exploit this in the chemoselective reduction of enones (entries 14, 15), although cyclohexenone and cyclohexanone have low reactivity with this system. While highly chemoselective, entry 15 highlights a weakness of the method, which is that cyclohexanone and cyclopentanone substrates are low-yielding in our hands.

We also explored the activity of the complex **1** towards a collection of aldehydes. Benzaldehyde and 4-hydroxybenzaldehyde were reduced (entries 16, 17). Complex **1** has lower activity for heterocyclic aldehydes, possibly due to coordination of the heterocycle to the iridium center competing with H_2. While **1** operates efficiently with many substrates, we sought a faster and more efficient catalyst to address cases that are not well-served by **1**. Suspecting that carbonylation in **1** reduces the basicity of the intermediate that must receive a proton in the slow step, we designed and synthesized chloride-substituted pre-catalyst (CN)IrCl(CO), **6**. Single crystals of **6** were prepared from slow liquid diffusion of dichloromethane and diethyl ether to enable determination of its molecular structure (Scheme 2). Unlike Nozaki's pincer iridium system [κ^3-[2,6-(^{i}Pr$_2$PCH$_2$)$_2$(C$_6$H$_3$N)]IrH$_3$], which takes 20 hours to form its active iridium trihydride complex,[18] precursor **6** immediately transforms to trihydride **7** at ambient temperature and pressure (see Supporting Information). While it is somewhat less shelf-stable than **1**, we find that complex **6** enables more rapid reactions than **1**. Table 1 shows compared yields of hydrogenations with catalysts **1** and **6** in which the more rapid reactivity of **6** enables significantly superior performance.



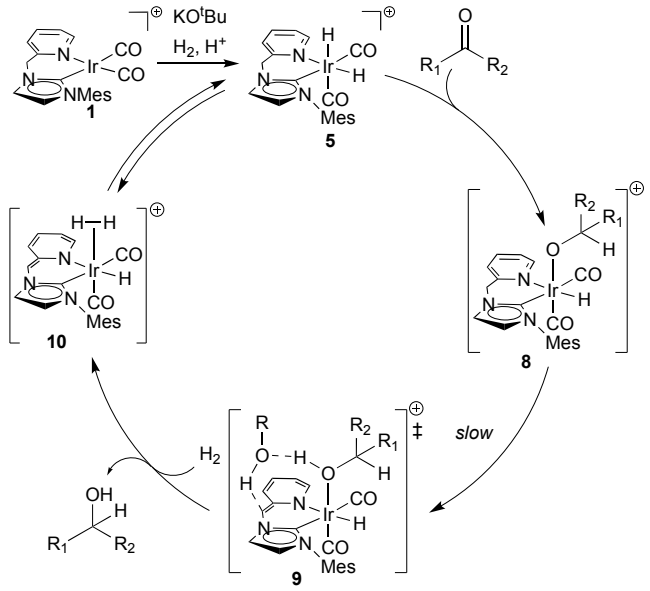
6 **7**

Scheme 2 Catalyst precursor **6** and iridium trihydride **7**.[18] ORTEP diagram of **6** (CCDC 2258133) with 50% ellipsoids.

A series of experiments were conducted to establish the reaction mechanism. We have measured the kinetic order of reaction for ketone, base, and catalyst and each is first order. We performed a kinetic isotope effect study by parallel reactions with complex **1** and benzophenone to investigate whether the H_2 coordinating step is rate-limiting. The observed KIE value of 1.06(11) is inconsistent with a kinetically relevant step involving H_2 metal complex coordination and cleavage; these typically have KIE > 2.[19] Further, hydrogen pressure does not effect this reaction rate. An Eyring plot, constructed using acetone as the substrate over a temperature range of 60-90 °C results in $\Delta S^{\ddagger}$ = -42.7(25) cal mol^{-1} K^{-1} and $\Delta H^{\ddagger}$ = 9.5(7) kcal mol^{-1} (see Supporting Information). This indicates a very low enthalpic (bond cleavage) component, but a significant entropic cost, in or before the rate-limiting transition state. We see this body of data as consistent with a reversible H_2 activation and a fast, facile hydride transfer early in the mechanism, both preceding a slow proton transfer to alkoxide or alcohol dissociation step. While the strong $\Delta S^{\ddagger}$ fits with rate-limiting gas activation, kinetic independence of [H_2] leads us to explain this as an intramolecular proton shutte. Thus, the ratio of reaction rates with and without added alcohol, $k_{iPrOH}/k_{no\ iPrOH}$ = 1.625, illustrates that added isopropanol accelerates the reaction overall, which is consistent with a role of for the alcohol as a proton shuttle in a rate-limiting proton transfer. In our previous work, we calculated the energetic advantage of such a proton shuttle in ketone hydrogenation by an analogous bifunctional iridium complex.[20]

We advance the mechanistic hypothesis shown in Scheme 3. We propose that species **5** transfers a hydride to substrate in a kinetically invisible step to form proposed intermediate **8**. Then, a kinetically relevant proton transfer from the catalyst's methylene arm to the alkoxide occurs. We suspect that an equivalent of alcohol or the protonated conjugate acid of the base is involved in this step as a proton shuttle, sketched as **9**. A neutral alcohol is then formed and released. We propose that the slow step is in this proton transfer/ alcohol dissociation sequence. Next, we believe that H_2 coordinates to the

dearomatized iridium species to form a structure like **10**. A proton can then be transferred from H_2 to the ligand backbone to regenerate the aromatized iridium-dihydride **5** in a reaction analogous to the one we observe stoichiometrically in scheme 1. Again, a proton shuttle would be logical.



Scheme 3 Proposed mechanism of catalysis.

In conclusion, we have developed efficient iridium catalysts **1** and **6** for the hydrogenation of ketones and aldehydes at ambient pressure. Importantly, finding a kinetic scheme in which H_2 is zero order enables facile ambient pressure reactions, which avoid the use of expensive autoclave reactors that are not readily available in every lab. Further, reactions can be accomplished using traditional Schlenk techniques without need for a glove box or freeze-pump-thaw conditions. These attributes improve the safety and operational convenience of the reaction. Complex, **6**, which differs from **1** by substitution of a CO for a chloride, has higher catalytic hydrogenation reactivity, affording useful results for some systems that are not easily reduced with **1**. We envision these catalysts as useful tools both for organic synthesis at scale, where the by-product of $NaBH_4$ or $LiAlH_4$ reduction creates operational costs and challenges, or small-scale practitioners needing to eliminate by-product separation, as in radiopharmaceutical synthesis.

Conflict of interest

TJW and ZL are co-founders of a company, Catapower Inc, which sells complexes **1**-**3**.

Acknowledgements

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